REMARKS

Claims 32-34, 36, and 39-82 are currently pending in the Application. Applicants note with appreciation that a number of prior rejections have been withdrawn. In the Office Action mailed September 3, 2008, the Examiner maintained the following rejections:

1. Claims 32, 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, *et al.*, J. Mol. Diagn. 2000 May 2(2):97-104, (hereinafter "Ledford") in view of U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau");
2. Claims 33, 36, 44-47, 58, 59, and 62, and 68-71 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, in view of Lane and in view of Lau, further in view of Morris, *et al.*, J. Clin. Microbiol., 1996 Dec., 34(12):2933-6, (hereinafter "Morris");
3. Claims 42, 43, 66, and 67 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, further in view of Marras, *et al.*, Genet Anal. 1999 Feb., 14(5-6):151-6 (hereinafter "Marras"); and
4. Claims 55, 56, 79 and 80 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, in further view of U.S. Patent No. 5,985, 563 to Hyldig-Nielsen, *et al.*, (hereinafter "Hyldig-Nielsen").

The Claims Are Not Obvious

1. Claims 32, 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, *et al.*, J. Mol. Diagn. 2000 May 2(2):97-104, hereinafter "Ledford" in view of U.S. Patent No. 5,770,365 to Lane, *et al.*, (hereinafter "Lane") in view of Lau, *et al.*, Science 294:858-862 (2001)(hereinafter "Lau").

As the Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that an Examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art."

See In re Wada and Murphy, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including … ascertaining the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Section 904 of the MPEP instructs Examiners to conduct an art search that covers "the invention *as described and claimed*." (emphasis added). Lastly, Applicants respectfully direct attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See In re Wada and Murphy*, *citing CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

As Applicants noted in the Amendment and Response filed on May 7, 2008, Ledford teaches the detection of genomic DNA using the two step Invader technology (see, *e.g.*, the title, and Figure 1). In the first step, a DNA probe and a DNA Invader oligonucleotide hybridize to the target DNA to form a first invasive complex, which is cleaved by the Cleavase cleavage agent (Fig. 1). In the second invasive complex, a release DNA flap from the first probe hybridizes to FRET-labeled DNA hairpin probe (Fig. 1) to form a second invasive complex. The portions of the Factor V gene hybridized to the detection oligonucleotides taught by Ledford were 55 nucleotides in length (page 100, column 1).

In the Office Action mailed September 3, 2008, the Examiner admits that Lane does not teach disassociating a target nucleic acid from a probe (Office action page 6) but asserts that Ledford is relied upon to demonstrate disassociating of a target nucleic acid from a probe. Applicants respectfully disagree that reliance on Ledford for the general

principles of disassociation of probe-target complexes cures the deficiencies of the combination, as discussed in the Amendment and Response submitted on May 7, 2008. Nonetheless, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claims 32 and 57 are amended to recite the hybridization of a microRNA with an unlabeled hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex between said microRNA and said hairpin probe, and to further recite disassociating said microRNA from said unlabeled hairpin probe, wherein said disassociating comprises disassociation of an RNA-DNA heteroduplex. Claims 32 and 57 are further amended to recite that the microRNA is less than 30 nucleotides in length.

Support for an RNA detection structure comprising an RNA-DNA heteroduplex between a microRNA and an unlabeled hairpin probe is found thoughout the specification. For example, Figures 24 and 25 shows several structures comprising microRNA hybridized to hairpin probes to form RNA detection structures comprising RNA-DNA heteroduplexes. The specification at page 24, line 4 recites target molecules of fewer than 30 nucleotides in length.

Neither Ledford nor Lane teach or suggest disassociating a microRNA from an unlabeled hairpin probe, nor does either reference teach disassociation of an RNA-DNA heteroduplex prior to detection of the formation of the RNA detection structure.

Lau discloses microRNAs in general but does not cure the deficiencies of the combination of Ledford and Lane, as Lau does not teach or suggest disassociating a microRNA from an unlabeled hairpin probe, nor does it teach disassociation of an RNA-DNA heteroduplex prior to detection of the formation of the RNA detection structure..

While Applicants do not acquiesce that other conditions necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Ledford, Lane and Lau does not teach or suggest all the elements of Claims 32 and 57, or the claims depending therefrom, *i.e.*, Claims 34, 35, 37-41, 48-54, 60, 61, 63-65, 72-74, 76, 77, 81 and 82. The cited art therefore fails to establish prima facie obviousness of these claims and Applicants respectfully request that these rejections be withdrawn.

2. Claims 33, 36, 44-47, 58, 59, and 62, and 68-71 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford, Lane, and Lau, further in view of Morris. Morris teaches the use of reverse transcription PCR for the detection of HCV RNA.

Applicants discuss the shortcomings of the combination of Ledford, Lane and Lau above. Morris fails to cure the deficiencies of the combination of Ledford, Lane, and Lau. As discussed above, Claims 32 and 57 recite the hybridization of a microRNA with an unlabeled hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, and further recite disassociating said microRNA from said unlabeled hairpin probe, wherein said disassociating comprises disassociation of an RNA-DNA heteroduplex. Morris does not teach or suggest either formation of an unlabeled RNA detection structure from a microRNA and a hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, nor does Morris recite disassociating a microRNA from an unlabeled hairpin probe, wherein the disassociating comprises disassociation of an RNA-DNA heteroduplex. Thus, the combination of Ledford, Lane, Lau and Morris fails to teach each element of Claims 33, 36, 44-47, 58, 59, and 62, and 68-71, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

3. Claims 42, 43, 66, and 67 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, further in view of Marras. Marras teaches the use of molecular beacon probes in multiplex detection of nucleic acids.

Applicants discuss the shortcomings of the combination of Ledford, Lane and Lau above. Marras fails to cure the deficiencies of the combination of Ledford, Lane, and Lau. As discussed above, Claims 32 and 57 recite the hybridization of a microRNA with an unlabeled hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, and further recite disassociating said microRNA from said unlabeled hairpin probe, wherein said disassociating comprises disassociation of an RNA-DNA heteroduplex. Marras does not teach or suggest either formation of an

unlabeled RNA detection structure from a microRNA and a hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, nor does Marras recite disassociating a microRNA from an unlabeled hairpin probe, wherein the disassociating comprises disassociation of an RNA-DNA heteroduplex. Thus, the combination of Ledford, Lane, Lau and Marras fails to teach each element of Claims 42, 43, 66, and 67, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

4. Claims 55, 56, 79 and 80 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ledford in view of Lau and in view of Lane, in further view of Hyldig-Nielsen. Hyldig-Nielsen discloses the detection of ribosomal RNA using peptide nucleic acid probes.

Applicants discuss the shortcomings of the combination of Ledford, Lane and Lau above. Hyldig-Nielsen fails to cure the deficiencies of the combination of Ledford, Lane, and Lau. As discussed above, Claims 32 and 57 recite the hybridization of a microRNA with an unlabeled hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, and further recite disassociating said microRNA from said unlabeled hairpin probe, wherein said disassociating comprises disassociation of an RNA-DNA heteroduplex. Hyldig-Nielsen does not teach or suggest either formation of an unlabeled RNA detection structure from a microRNA and a hairpin probe to form an unlabeled RNA detection structure comprising an RNA-DNA heteroduplex, nor does Hyldig-Nielsen recite disassociating a microRNA from an unlabeled hairpin probe, wherein the disassociating comprises disassociation of an RNA-DNA heteroduplex. Thus, the combination of Ledford, Lane, Lau and Hyldig-Nielsen fails to teach each element of Claims 55, 56, 79 and 80 and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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